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## REPLY: Platelets Interplay Between Pneumonia and Cardiovascular Events

### Establishing a Link?

## Platelet Activation and Myocardial Infarction in Patients With Pneumonia

### Are Statins the Answer?

We thank Dr. Gavrillaki and colleagues for the comments related to our recent paper (1) demonstrating a significant association between in vivo platelet activation and myocardial infarction (MI) in 278 patients affected by community-acquired pneumonia (CAP) and suggesting a potential role for platelets in precipitating coronary ischemia.

Dr. Gavrillaki and colleagues raise some issues that need to be addressed. The authors question the putative interplay between infections and MI overall because interventional trials with antibiotics failed to show a reduction of MI. However, trials with antibiotics have serious clinical and methodological limitations regarding dosages of the antibiotics, wide variation in sample size and follow-up, and limited use of antibiotics (essentially macrolides and fluoroquinolone) (2). Furthermore, interventional trials with antibiotics have been performed in patients with stable or acute coronary heart disease on the assumption that microorganisms, in particular *Chlamydia pneumoniae*, are implicated in atherosclerosis initiation and progression (2).

Hence, it is methodologically inappropriate to extrapolate from these findings that infections cannot precipitate MI because these clinical settings are different in terms of clinical course, concomitant treatment, and very likely, mechanism of disease from CAP-related MI. In this context, it is clinically relevant that pneumonia severity score was a strong predictor of MI, indicating that the severity of infection and/or inflammation plays a key role in favoring myocardial ischemia. Platelet activation may be one mechanism through which CAP precipitates MI via a process of coronary thrombosis and/or vasoconstriction. We don't have conclusive data on this issue, but it is interesting to underscore that most patients with CAP disclosed non-ST-segment elevation MI, indicating that type II MI and, therefore, coronary vasoconstriction might have an important role in favoring myocardial ischemia. We agree with the authors that the concomitant presence of cardiovascular disease or atherosclerotic risk factors could account for platelet activation detected at admission, but its significant reduction, observed at discharge, points to a role of CAP in favoring platelet activation. The mechanism(s) accounting for CAP-related platelet activation were not investigated in the study and consequently may be only a matter of speculation. Analysis of more sophisticated markers of platelet activation will certainly help to provide more insight into the role of platelets as a determinant of myocardial ischemia in pneumonia. However, we believe that at this moment, it is more crucial to know whether platelet activation represents a mere epiphenomenon of CAP or has a role in triggering coronary thrombosis and/or vasoconstriction. Thus, interventional trials with aspirin or other antiplatelet drugs could be of interest to investigate whether platelets actually have a role in precipitating MI in patients with pneumonia.

Interestingly, Dr. Khan and colleagues, in their letter, suggest that statins may be an intriguing alternative because they possess antiplatelet activity, and a recent meta-analysis demonstrated a potential role of statins in reducing CAP-related mortality (3). We agree with this hypothesis because statins disclose an early and late antiplatelet effect, which is mediated by down-regulation of Nox2-derived oxidative stress and lipid-lowering activity, respectively (4). Nox2 down-regulation may be of interest because in patients with CAP Nox2, the most important cellular producer of oxygen free radicals, is up-regulated and associated with myocardial damage and ischemia (5). Furthermore, statins amplify the platelet response to aspirin by reducing platelet eicosanoid formation, namely isoprostanes and thromboxane A2, and could, in turn, be useful in case of incomplete COX1 inhibition by aspirin (4). Hence, statins may be tested as an alternative to aspirin or on top of aspirin to assess whether they are able to reduce cardiac complications in patients with CAP.

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## REPLY: Platelets Interplay Between Pneumoni | Cardiovascular Events

### Establishing a Link?

We appreciate the interest by Dr. Gavrillaki and colleagues in our editorial and their insightful comments.

First of all, Dr. Gavrillaki and colleagues indicate that we support the infection hypothesis for atherosclerosis. We do not support such hypothesis, and thus, this affirmation was not stated in our editorial. We do believe the role of inflammatory processes (not necessarily infective) in the genesis and progression of atherosclerosis (1). In fact, a variety of systemic proinflammatory conditions increase the risk of atherosclerotic cardiovascular events, including rheumatoid arthritis, systemic lupus erythematosus, or psoriatic arthritis (2). Furthermore, atherosclerosis is aggravated by systemic inflammation of any etiology, as the one seen after myocardial infarction (MI) (3). It is in this context of atherosclerosis as a systemic inflammatory disease (but never of atherosclerosis as caused by microorganisms) where our comments about the pathophysiological link between community-acquired pneumonia (CAP) and MI should be placed. It is the systemic inflammatory response originated by CAP and influenza infection (and not the microorganism per se) that most likely aggravates atherosclerosis burden and contribute to the destabilization of atheroma plaques, thus increasing the risk of MI. In fact, we do agree with Dr. Gavrillaki and colleagues in the microorganism theory having been refuted long ago (4).

Second, Dr. Gavrillaki and colleagues consider the increased platelet activation in CAP patients developing MI because of the comorbidities of those patients, and thus already present even before the CAP. Notwithstanding, Cangemi et al. (5) adjust in the multivariate analysis for those baseline (i.e., pre-CAP) comorbidities (age, sex, body mass index, diabetes, hypertension, renal failure, previous MI or stroke, peripheral artery disease), and they also test for collinearity, so we can conclude that enhanced platelet reactivity in CAP patients is independently associated with MI even after adjusting for those baseline comorbidities. That platelet aggregation is a risk marker or a risk factor is a different story that cannot be demonstrated statistically, only by trial evidence, demonstrating that altering the risk factor (platelet aggregation in CAP) changes the prognosis (MI).

Finally, we do agree with Dr. Gavrillaki and colleagues regarding that platelet reactivity, not aggregation, was assessed in the study by Cangemi et al. (5). As they suggest, the monocyte-platelet aggregates (MPA) are one marker of platelet activation that could shed additional information on the link between platelet activation in CAP and MI. However, heterotypic platelet aggregation (of which MPA is the prime example) is not the only parameter to assess/study platelet activation. Other markers such as homotypic platelet aggregation (by light-transmission aggregometry) or soluble serum markers (such as the P-Selectin, CD40L, or TXB2 that Cangemi et al. [5] used) are universally established/accepted, so the choice of a specific marker does not change the hypothesis-generating message of this article. Future studies will undoubtedly analyze additional markers of platelet activation (including MPA) to profile in depth the postulated mechanistic role of increased platelet reactivity in MI incidence among CAP patients.